REMARKS

Claims 1-18, 20-37, and 51 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation that the amendments filed December 18, 2003 have been entered.

2. Claims 1, 4-18, 20-28, and 32-37 are provisionally rejected under 35 U.S.C. 101 for allegedly claiming the same invention as that of claims 1, 4-18, 22, 24, 27, and 33 of copending Application Serial No. 09/831,096. Applicants traverse this rejection.

Applicants note that substantive prosecution of copending Application Serial No. 09/831,096 has commenced. Applicants submit that actions taken during substantive prosecution of the copending application will obviate the rejection, and that the Examiner will be able to independently verify this prior to the issuance of any further Office communication. Reconsideration and withdrawal of this rejection are requested.

3. Claims 1-3 and 29-31 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-50 of copending Application Serial No. 09/831,096. Applicants traverse this rejection.

As outlined above, Applicants note that substantive prosecution of copending Application Serial No. 09/831,096 has commenced, and that actions taken during substantive prosecution of the copending application will obviate the rejection. Applicants note that, if necessary, Applicants will submit a terminal disclaimer upon indication of allowable subject matter.

4. Claims 32 and 33 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to practice the claimed invention. Applicants traverse this rejection.

Today and as of the filing date of the instant application, the making of transgenic animals was sufficiently routine and well known in the art to moot the Examiner's concerns. Furthermore, the relevant question is not whether Applicants have correlated expression of a

transgene with induction of a disease state, as that is not the most relevant use of CAB domain expression in a transgenic animal. The CAB domain is a man-made fusion domain and is not associated with any disease. The CAB domain was designed to be a drug-binding domain for use as a component of a ligand-regulated switch mechanism. Applicants have certainly enabled this use. Furthermore, the art provided extensive guidance and examples whereby other related biological switches were successfully expressed in cells and in transgenic animals.

Transgenic animals expressing other types of biological switches had been made prior to the filing of the present application. These include transgenic animals expressing closely related biological switches (e.g., the Schreiber & Crabtree-style dimerization-based switches), as well as transgenic animals expressing less closely related switches (e.g., tetracycline-based switches).

To briefly illustrate the advanced state of the art in the making of transgenic animals expressing related biological switches, Applicants did the following search for references relevant to transgenic animals and tetracycline-based biological switches: http://scholar.google.com/scholar?q=transgenic+%28mice+OR+mouse%29+tetracycline+&ie=UTF-8&oe=UTF-8&hl=en&btnG=Search. This search uncovered approximately 4000 references dealing mostly with transgenic mice engineered to express tetracycline based biological switches. Specifically, these mice express a transgene for a tetracycline system fusion protein which, in the presence of tetracycline or the tetracycline analog doxycycline, induce ectopic expression of a target gene in tissue in the mice. By way of example, Applicants enclose herewith a few of the references identified in the above search (Kistner et al., 1996, PNAS 93: 10933-10938; St-Onge et al., 1996, Nucleic Acids Research 24: 3875-3877; Furth et al., 1994, PNAS 91: 9302-9306; enclosed herewith as Exhibits 1-3).

Similarly, upon a brief search of the literature, Applicants readily identified a number of references illustrating transgenic animals expressing various dimerization-based switches analogous to the presently claimed CAB constructs. By way of example, Applicants enclose herewith a few references that teach the making and use of transgenic animals expressing various dimerization-based molecular switches (Soldevila et al., 2001, Cellular Immunology 214: 123-138; Mallet et al., 2002, Nature Biotechnology 20: 1234-1239; Freeman et al., 2003, Cancer Research 63: 8256-8263; Kazansky et al., 2003, Cancer Research 63: 8757-8762; enclosed herein as Exhibits 4-7).

The Examiner has taken a few phrases from references published significantly prior to the filing of the present application to support a hypothetical concern that the invention might not work. Surely, concerns supported by outdated art are dispelled by the actual successes attained by others who made and used transgenic animals expressing highly analogous constructs (e.g., other molecular switch-type constructs). Accordingly, Applicants contend that claims 32 and 33 are enabled throughout their scope.

Applicants contend claims 32 and 33 are enabled throughout their scope. However, to further clarify that cells comprising the CAB constructs of the invention also express the composite proteins encoded by these nucleic acid constructs, Applicants have amended claims 26 and 27 (e.g., the claims from which claims 32 and 33 depend). Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

5. Claims 26-31 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants traverse this rejection.

The Office Actions states that "the specification, while being enabling for an isolated host cell in vitro comprising a nucleotide sequence encoding a CAB domain and methods for producing genetically engineered host cells in vitro, does not reasonably provide enablement for is not enabling for a host cell in vivo comprising a CAB domain protein." (Office action, page 8). As above, the Examiner appears to base this rejection on (i) the mistaken assumption that the sole purpose of these composite constructs is to mimic or ameliorate disease symptoms and (ii) a reliance on a small number of relatively old references that question the enablement of the presently claimed invention. Applicants contend that these provide an insufficient and inappropriate basis to reject the presently claimed invention.

In contrast to the hypothetical concerns raised in the Office Action, Applicants have cited (see above) numerous articles that demonstrate that related molecular switches had been and continue to be readily expressed both in vitro and in vivo. Furthermore, the instant application was filed several years after many of the references cited by the Examiner, and thus the general level of skill in the art of molecular biology was higher than at the time of publication of many of the references relied on by the Examiner. In light of the high level of skill in the art, as evinced by the successful in vitro and in vivo use of related molecular switches, Applicants contend that

the claims are enabled throughout their scope. The actual successful use of related constructs in vivo and in vitro outweighs any hypothetical concern that the invention might not work.

In addition to the concerns outlined above, the Examiner specifically rejected claims 30 and 31 because the specification allegedly enables only in vitro methods for transforming an isolated somatic cell. Applicants are confused about the nature of this rejection. Claims 30 and 31 specifically recite that the claimed methods are ex vivo methods. Given that the terms "in vitro" and "ex vivo" are synonymous, Applicants don't understand the basis of the rejection.

To help dispel any possible confusion, Applicants will briefly reiterate some of the arguments of record that Applicants believe address this rejection. Applicants direct the Examiner's attention to the following exemplary passages from the specification that demonstrate the variety of uses for cells expressing the subject constructs, as well as methods for expressing the subject constructs in cells (see, e.g., page 2, lines 4-10; page 3, line 31-page 4, line 7; page 4, line 27-page 5, line 3). Furthermore, Applicants have not merely described the subject methods, Applicants have provided working examples that demonstrate methods of expressing the constructs of the present invention in cells (see, Examples 4, 5, 8, etc.). Applicants' working examples demonstrate that the subject constructs can be expressed in cells, and further that the genetically engineered cells express functional proteins that are regulatable.

Applicants contend that the specification provides extensive guidance and working examples to enable one of skill in the art to practice the claimed invention. As outlined in MPEP 2164. "As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." MPEP 2164.01(b); *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970). Applicants contend that disclosure of working examples representative of subject matter within the scope of the pending claims clearly satisfies the requirements under 35 U.S.C. 112, first paragraph. Maintenance of his rejection not only deprives Applicants of reasonable patent protection based on the disclosure; maintenance of this rejection actually deprives Applicants of protection for the very working examples explicitly disclosed in the specification. Clearly, such a result is inconsistent with the MPEP, case law, and the purpose of the patent system.

In light of Applicants' disclosure which bears a reasonable correlation to the scope of the pending claims, and in light of the well developed art in the making and using of genetically

modified cells and organisms, Applicants contend that the pending claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection are respectfully requested. If the Examiner maintains this rejection, Applicants respectfully request clarification.

6. Claims 1-6, 20-21, 26, 34, and 36 are rejected under 35 U.S.C. 102(b) as allegedly anticipated by Mondragon et al. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

To anticipate, a prior art reference must teach each and every limitation of a claim. *Verdegaal Bros v. Union Oil Company of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP 2131. Mondragon et al. fail to satisfy this requirement, and thus fail to anticipate the claimed invention.

The claims are directed to nucleic acids encoding a CAB domain comprising a portion of calcineurin A and a portion of calcineurin B. As defined and illustrated in the specification, a CAB domain is a composite ligand binding domain comprising a portion of calcineurin A and a portion of calcineurin B (page 27, line 7-10). Furthermore, the term "composite" clearly refers to a fusion protein where the two or more portions are covalently linked (page 9, lines 17-28). Accordingly, one of skill in the art would readily appreciate that the claimed nucleic acids encode composite proteins comprising portions of calcineurin A and calcineurin B that are linked to one another.

In contrast to the nucleic acids encoding the composite proteins of the present invention, Mondragon et al. provide reagents for expressing calcineurin A and calcineurin B as **separate** proteins, and not as a composite protein. Mondragon et al. generated a tandem expression construct including a portion of calcineurin A and a portion of calcineurin B (pETCNa; figure 2). However, the tandem expression construct of Mondragon et al. does not encode a fusion/composite protein. Note that the calcineurin A and calcineurin B sequences in Mondragon et al. are each preceded by their own Shine/Dalgarno sequence. Note further that the construct taught by Mondragon et al. is expressed in the prokaryote E. coli. Expression of a tandem expression construct containing two separate Shine/Dalgarno sequences in E. coli generates two distinct (e.g., not covalently linked) proteins. Although, once expressed, the calcineurin A and calcineurin B proteins produced by Mondragon et al. may associate, such an

association is distinct from and fails to anticipate claims directed to nucleic acids encoding a single composite protein.

Applicants contend that, in light of the specification, the term "CAB domain" clearly refers to a composite protein comprising a portion of calcineurin A and a portion of calcineurin B, and that Mondragon et al. fail to anticipate a nucleic acid encoding a CAB domain. Nevertheless, to expedite prosecution, Applicants have amended the claims to more explicitly point out that the claimed nucleic acids encode composite proteins. Applicants' amendments are not in acquiescence to the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope.

Mondragon et al. provided an improved method for co-expressing, *as separate protein sub-units*, calcineurin A and calcineurin B. However, Mondragon et al. fail to teach or suggest constructs for expressing calcineurin A and calcineurin B as a composite/fusion protein, as presently claimed. Given that Mondragon et al. fail to teach or suggest each and every limitation of the pending claims, Mondragon et al. fail to satisfy the requirements necessary to undermine the patentability of the claimed invention. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945, under Order No. APBI-P01-385.**

Respectfully Submitted,

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